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BIOLOGICALLY-BASED THERAPY IN WALDENSTROM'S MACROGLOBULINEMIA

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Rituxan in combination with various chemotherapeutic regimens have achieved remissions in patients with Waldenstrom's macroglobulinemia (WM) and prolonged duration of remission. However, ultimately patients experience disease progression and there is no cure. Novel therapeutic interventions for this disease are therefore needed to specifically target the malignant cell. The potential susceptibility of myeloma cells as well as, in small number of patients, lymphoplasmacytic cells from WM to immune based therapies have been demonstrated following allogeneic transplantation through graft versus tumor effect. A focus of investigation therefore has been the use of immune-based therapies in multiple myeloma (MM) and WM to decrease the risk of progression and potentially achieve curative outcomes. To this end we have identified novel CD19 and CD20 antigen-derived HLA-A2.1-specific immunogenic peptides, $CD19_{150-158}$ (KLMSPKLYV) and $CD20_{188-196}$ (SLFLGILSV), for generating cytotoxic T lymphocytes (CTLs) against malignant B-cells. Initial testing showed that the CTLs displayed antigen-specific and HLA-A2.1-restriced cytotoxic activity against both Burkitt's lymphoma and chronic lymphoid leukemia cell lines. The observed cytotoxic activity of the CTLs was shown to be specific to the $CD19_{150-158}$ or the $CD20_{188-196}$ peptides. Additionally, the CTLs displayed a significant ($p<0.05$) increase in cell proliferation and IFN-γ release following re-stimulation with HLA-$A2.1^+$/$CD19^+$/$CD20^+$ tumor cell lines. We have now evaluated the activity of the CD19 and CD20 peptide specific-CTLs against several multiple myeloma cell lines. CD19 peptide specific-CTLs generated from normal donors were able to specifically lyse $CD19^+$/HLA-$A2.1^+$ MM cell lines (30% lysis; 10:1 E: T ratio) but did not lyse $CD19^-$/HLA-$A2.1^+$ or $CD19^+$/HLA-$A2.1^-$ cell lines. Similarly, the CD20-specific CTLs generated from normal donors lysed $CD20^+$/HLA-$A2.1^+$ MM cell lines (25% lysis; 10:1 E:T ratio), in a manner restricted to HLA-A2.1 and specific to antigens. We have next showed IFN- production by the CTLs after exposure to $CD19^+$/HLA-$A2.1^+$ or $CD20^+$/HLA-$A2.1^+$ MM cells. Moreover, we are able to expand CD20/CD19-CTLs under serum-free culture conditions while maintaining their cytotoxic activity. In ongoing studies, we are evaluating the ability of CD19- and CD20-specific CTLs to eliminate in vitro lymphoplasmacytic cells from patients with WM and also evaluating their efficacy in a SCID mouse model of myeloma and WM. Additionally, our emerging data shows that Thalidomide (Thal) and its more potent analogues immunomodulatory drugs (IMiDs) co-stimulates T-cells via CD28-B7 pathway providing the cellular and molecular basis for use of IMiD3 as an adjuvant to enhance immune responses following vaccination. These preclinical studies strongly support the use of the immunogenic CD19 and CD20 peptide-based vaccines along with immunomodulatory agents as a promising immunotherapeutic approach in WM.